REMARKS/ARGUMENTS

Reexamination and reconsideration of this Application, withdrawal of the rejection, and formal notification of the allowability of all claims as now presented are earnestly solicited in light of the above amendments and remarks that follow. Claims 2, 3, 12-21, and 35-38 are pending in the application.

All pending claims stand rejected as unpatentable under 35 U.S.C. 103(a) over the combined teachings of the U.S Patent No. 5,484,601 to O'Leary et al., U.S. Patent No. 5,385,887 to Yim et al., and U.S. Patent No. 6,030,635 to Gertzman et al. Applicants continue to traverse this rejection.

Applicants respectfully submit that one of ordinary skill in the art would have no motivation to combine the three references of the rejection in the manner contemplated by the Examiner. Specifically, there is no motivation to combine the calcium sulfate hemihydrate of Yim with the teachings of O'Leary. The O'Leary reference is directed to a flowable demineralized bone powder composition comprising demineralized bone powder in an organic liquid carrier, such as glycerol. It is clear that this reference is directed to compositions that are intended to maintain a certain consistency for an extended period of time. Although this consistency is described as widely varying, there is nothing in O'Leary to indicate that a composition that hardens or sets over time is envisioned. In fact, the reference suggests otherwise by describing the term "flowable" as including compositions with consistencies ranging from those that are "shape sustaining but readily deformable . . . to those which are runny" (column 3, lines 30-34). Further, we note that O'Leary suggests the use of a thickener if settling of the bone powder within the organic liquid is a problem (column 3, lines 56-63). This also suggests that the composition is intended to maintain a liquid, flowable state for an extended period of time. Obviously, if the composition is intended to set into a hardened mass within a short period of time, settling would not be an issue. Additionally, the O'Leary reference suggests that the composition described therein can be prepared "well in advance and stored under sterile conditions until required for use" (column 4, lines 34-37; See also, column 1, lines

63-66). This also suggests that the flowable compositions envisioned by O'Leary maintain a uniform flowable consistency for an extended period of time.

All of the above teachings of O'Leary are manifestly inconsistent with the well-known properties of calcium sulfate hemihydrate solutions. As described in the references discussed in the background section of the present application, prior to Applicants' present invention, calcium sulfate hemihydrate was used in certain bone graft compositions where it was understood that the composition would harden or set rather quickly as the calcium sulfate hemihydrate reacted with water to form the dihydrate form. Since it was known in the art that calcium sulfate hemihydrate would cause a composition to harden or set in a relatively short period of time, such as 5-10 minutes, the addition of calcium sulfate hemihydrate to the O'Leary composition would have been avoided by one of skill in the art since the resulting composition would not have been expected to maintain a flowable state for an extended period of time, which is clearly the aim of the reference. Yim itself describes how quickly a calcium sulfate hemihydrate solution loses flowability in Table 2 in column 10. Note that each tested composition appearing in Table 2 was non-flowable within 15 minutes. Better evidence against the combination of O'Leary and Yim could hardly be imagined.

Although Applicants have discovered that the claimed plasticizing substance can forestall the calcium sulfate hemihydrate hardening reaction in a bone graft substitute composition, this effect is not appreciated in the prior art. Yim purports to suggest compositions including both calcium sulfate hemihydrate and certain cellulosic materials that are described as protein sequestering agents. However, this combination does not appear in any examples and the Yim reference obviously does not appreciate the handling advantages that Applicants have discovered since the reference consistently describes the calcium sulfate hemihydrate as a material that will reduce set-up time and describes numerous compositions in Table 2 that quickly harden or set. As a result, one of ordinary skill in the art without the benefit of Applicants' disclosure would view the combination of calcium sulfate hemihydrate with the O'Leary formulation as likely to negate the flowability requirement set forth in O'Leary. Thus, for this reason, one of ordinary skill in the art would not find the requisite motivation to combine the calcium sulfate hemihydrate of Yim with the O'Leary composition.

Even ignoring the clear suggestion in the art to avoid combining calcium sulfate hemihydrate with O'Leary as discussed above, the Examiner's reasoning for combining Yim with O'Leary is inconsistent with the teachings of the Yim reference. Yim describes the use of calcium sulfate to reduce the preparation time or "set up time" of a composition comprising osteogenic proteins, autogenous blood and a porous particulate polymer matrix material (column 2, lines 51-65). Presumably, calcium sulfate is useful in this composition to reduce setup time because of the relatively long period of time it takes for autogenous blood to clot in the formulation.

The Examiner relies on language in the Yim reference regarding reduction in set-up time and improvement in handling, moldability and consistency as evidence of a motivation to combine the calcium sulfate hemihydrate of Yim with the formulation of O'Leary. However, as noted above, Yim does not provide a general suggestion that calcium sulfate provides such advantages in all bone graft compositions. Instead, the Yim reference only suggests that a calcium sulfate hemihydrate-containing substance (CSHS) provides such advantages when combined with the formulation described in U.S. Pat. No. 5,171,579 (see column 2, lines 51-65). Yim only suggests a CSHS provides such advantages in the context of a formulation comprising osteogenic proteins, autogenous blood, and a porous particulate polymer matrix, such as a copolymer of lactic acid and glycolic acid (PLGA). There is no suggestion in the Yim reference that such improved properties would be expected in any other formulation. Yim merely teaches that, "[t]o reduce the preparation time and improve the above formulation's handling characteristics" (emphasis added), a CSHS can be added. The "above formulation" is the formulation described in the '579 patent, which includes an osteogenic protein, autogenous blood, and a porous particulate polymer matrix. Since the composition in the O'Leary reference is not a combination of osteogenic proteins with autogenous blood and a porous particulate polymer matrix such as PLGA, there would be no motivation to combine the CSHS of Yim with the composition described in O'Leary for the reasons suggested by the Examiner. The O'Leary formulation comprises demineralized bone powder and an organic liquid, and such a composition is markedly dissimilar to the composition described in Yim as needing improvement in set-up time, moldability, etc. Further, there is nothing in the O'Leary reference to suggest a

problem with moldability, consistency, etc. of the formulation described therein that might lead one of ordinary skill in the art to seek an additive to address such a problem. Indeed, the O'Leary patent seems to suggest that the consistency of the "flowable" material can be adjusted simply by altering the amount of the liquid component (column 3, lines 28-35).

The Examiner responded to this argument by noting that Yim describes the addition of calcium sulfate hemihydrate to other compositions as well, such as the suggestion at column 2, lines 27-31, to form a composition containing calcium sulfate hemihydrate and an osteogenic protein. Yet, the Examiner continues to rely on the improved handling/moldability teaching in Yim as the motivating factor for the alleged combination. The Yim reference does not teach that improved handling/moldability will be realized in the other embodiment noted by the Examiner. The osteogenic protein/calcium sulfate hemihydrate embodiment is described more fully at column 8, lines 16-28, where the reference teaches that, in that embodiment, calcium sulfate hemihydrate provides a structural matrix function, an osteoconductive matrix, and a protein sequestering function. There is no discussion of improved handling whatsoever. Thus, even ignoring the disincentive to use calcium sulfate hemihydrate in the O'Leary reference described above, the Yim reference fails to provide proper motivation to modify O'Leary in the manner contemplated by the rejection.

In addition, Applicants respectfully submit that there is no motivation to combine the teachings of the Gertzman reference with the teachings of O'Leary. The composition described in the Gertzman reference is so fundamentally distinct from the composition described in the O'Leary reference that one of ordinary skill in the art would view such differences as weighing against the combination suggested by the Examiner. The Gertzman reference is directed to a malleable paste for filling bone defects, the composition including a high molecular weight hydrogel and an aqueous solution as the carrier for demineralized bone powder. The O'Leary reference is clearly not directed to compositions including a high molecular weight hydrogel component as a carrier ingredient for demineralized bone, and for this reason, one of ordinary skill in the art would not view the teachings of Gertzman as relevant to the O'Leary composition.

Further, Applicants again note that the Gertzman reference specifically contrasts the teachings of the O'Leary reference. In the background section, the Gertzman reference points

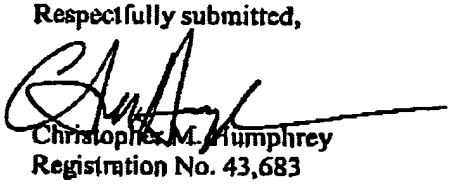
out numerous disadvantages associated with GRAFTON, a commercial embodiment of the composition of O'Leary. Additionally, Gertzman suggests "glycerol and other similar low molecular weight organic solvents are toxic and irritating" (emphasis added) (column 3, lines 22-23). The Examiner attempts to restrict the teaching away of Gertzman to only glycerol, but the above quote makes it clear that Gertzman teaches away from many low molecular weight organic solvents of the type described in O'Leary, not just glycerol.

For the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the rejection.

It is believed that all pending claims are now in condition for immediate allowance. It is requested that the Examiner telephone the undersigned should the Examiner have any comments or suggestions in order to expedite examination of this case.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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